Mortality among Industrial Workers Exposed to Phenol

Mustafa Dosemeci,[1] Aaron Blair,[1] Patricia A. Stewart,[1] Jerry Chandler,[1] and Michael A. Trush[2]

We conducted a follow-up study to evaluate mortality among 14,861 workers employed in five facilities producing or using phenol and formaldehyde. More than 360,000 person-years of follow-up accrued. Mortality rates from all causes of death combined were similar to those in the general U.S. population. We observed excesses of cancer of the esophagus, cancer of the kidney, and Hodgkin's disease among workers exposed to phenol, but none of these excesses showed a dose–response relation with exposure to phenol. Excess lung cancer mortality (SMR = 1.2) showed no consistent pattern by any exposure index. Workers exposed to phenol had lower mortality ratios for cancer of the buccal cavity and pharynx, cancer of the stomach, cancer of the brain, arteriosclerotic heart disease, emphysema, disease of the digestive system, and cirrhosis of the liver. Of these, arteriosclerotic heart disease, emphysema, and cirrhosis of the liver were inversely related to duration of phenol exposure and to cumulative phenol exposure levels. Although these inverse associations may be due to chance or uncontrolled confounders, the ability of phenol to interfere with the generation of oxidants in experimental systems suggests that the pattern may have biologic plausibility. (Epidemiology 1991;2:188–193)

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Phenol, a monohydroxy derivative of benzene, is among 50 major chemicals produced in the United States.[1] The National Institute for Occupational Safety and Health has estimated that approximately 10,000 workers are potentially exposed to phenol in its production, formulation, and distribution, and many more are exposed to the use of phenol.[2] Its reaction with formaldehyde to produce phenol-formaldehyde resins accounts for approximately 40% of phenol usage in the United States.[3]

The carcinogenicity of phenol has been evaluated in several tumor initiation-promotion studies.[4-7] In an early study,[4] a weak-to-moderate promoting action on mouse skin was found, following prior initiation with 7,12-dimethylbenz(a)anthracene (DMBA). Studies by Van Duuren and coauthors[5,6] concluded that phenol was not a cocarcinogen, but rather showed an inhibitory effect on mouse skin carcinogenicity of benzo(a)pyrene. Based on skin-painting studies of mice by the National Cancer Institute,[7] it was concluded that there is no clear evidence that phenol acts as a complete carcinogen, particularly at low exposure levels.[3] The chronic effects of phenol exposure in humans have not been investigated.

To assess the risk of cancer and other causes of death among industrial workers exposed to phenol, we conducted a mortality study using retrospective estimations of exposures to phenol in five phenol-formaldehyde resin plants.

Subjects and Methods

Five of ten companies from a National Cancer Institute mortality study of industrial workers exposed to formaldehyde[8] were included in this investigation; we chose these companies because of the extensive usage of phenol in their facilities. The cohort comprised all white male workers first employed at the five companies before January 1, 1966; it has been described in detail elsewhere.[8] Company records were abstracted to obtain basic demographic information and work histories for each subject. Subjects were traced to January 1, 1980, to determine vital status. The ascertainment of the vital status of subjects was carried out through the Social Security Administration, Health Care Finance Administration, Veterans Administration, credit bureaus, motor vehicle departments, and telephone directories. We obtained death certificates of deceased subjects; causes of death were determined by a nosologist, using the Eighth Revision of the International Classification of Diseases.

For the historical assessment of exposure to phenol, we used unique job/department/calendar-year combinations in each of the five phenol-using plants from the National Cancer Institute formaldehyde study. In this study, estimation of exposures to phenol was carried out semiquantitatively (none, low, medium, and high) for each unique job/department/calendar-year combination. Sources of

information available for estimating exposures to phenol consisted of industrial hygiene walk-through survey reports for each plant, historical monitoring results, and other workplace information on formaldehyde exposure.

We used semiquantitative exposure assessment method, the Job Function Evaluation, for estimating historical exposures to phenol.[9] The Job Function Evaluation method, a modified version of the uniform task categorization concept,[10] classifies job functions into seven major groups (production, maintenance, clean-up, technical, material handling, administrative, and isolated). For each functional group, a classification reflecting potential exposure level (I_k) was made, and weights were assigned to each level (none = 0, low = 1, medium = 4, and high = 9). In addition, potential exposure levels for plant (E_i) and area (E_j) were assigned using the same weights. For control measures (C_k), categories were weighted as effective control (0.1), moderate control (0.5), and no control (1.0); and for frequencies of exposure (F_k), they were weighted as occasional (0.1), frequent (0.5), and continuous (1.0). Relative weights of all these exposure parameters were estimated by an industrial hygienist who had conducted walk-through surveys at the study plants. The exposure score for each combination was calculated as follows[9]:

$$E_{ijk} = E_i * E_j (1 + I_k * C_k * F_k)$$

where:

E_{ijk} = exposure score for plant/area/job title/calendar-year combination,
E_i = overall exposure index for a particular plant (i),
E_j = overall exposure index for a particular area (j),
I_k = intensity of exposure for the job title (k),
C_k = effects of control measures on exposure for the job title (k), and
F_k = frequency of exposure for the job title (k).

Cumulative exposure for each subject was calculated by multiplying the exposure score (E_{ijk}) of each subject's job by the time spent in that job and summed across all jobs held by the subject. Cut points (<8 score-year; 8–79 score-year; 80–319 score-year; and 320+ score-year) for the cumulative exposure categories used in the analysis were generated to allow sufficient numbers in each category.

We used standardized mortality ratios (SMRs) and age-adjusted, directly standardized rate ratios (SRRs) to compare the mortality experience of phenol workers with that of the total U.S. population (SMRs) and nonexposed workers (SRRs). In the analysis, the calculation of SMRs and SRRs was carried out for white males only. Person-year accumulation began on January 1 of the initial year

of cohort entry, ranging from 1934 to 1951 for the various plants or the date of initial employment (whichever was later) and ceased at the closing date of the study, the date of death, or the last date known alive (whichever was earliest). SMRs were computed using a program developed by Marsh and Preininger.[11] Expected numbers were calculated by applying five-year age and calendar-year mortality rates of the referent population for the years 1930 to 1980. Ninety-five percent confidence intervals (CI) were calculated by using the method of Bailar and Ederer.[12] Subjects could contribute person-years to more than one exposure category. Person-years accumulated in the exposure category of the first job until the subject's cumulative exposure or duration exceeded the upper limit for that stratum, when accumulation would begin in the next higher category.

Results

The demographic and exposure characteristics of the cohort subjects are presented in Table 1. Of the 14,861 white males included in this study, 12,172 were waged, 2,018 were salaried, and 671 were "other status." Among all white males and all wage white male workers, the nonexposed category constituted approximately 40% of the cohort, whereas 6–10% of the cohort fell in the highest cumulative exposure level. Many subjects (58% for all white males, 61% for all wage white males, and 36% for wage-earning white males employed more than a year) were employed five years or less, and about 40% were employed one year or less. A majority of workers first entered the cohort after 1946 (80%, 82%, and 77%, respectively), and most workers (72%) were less than 30 years old when they entered the study. Follow-up was 97% complete, and approximately 360,000, 290,000, and 180,000 person-years of risk were accumulated by all white males, by all wage-earning white males, and wage-earning white workers employed more than a year, respectively. The proportion of deceased subjects was similar among all white males (21%), wage-earning white males (22%), and among wage-earning white males employed more than a year (23%).

Mortality from all causes of death among the entire cohort (Table 2) was as anticipated (SMR = 1.0) for white males. Deficits in mortality were observed for infective and parasitic disease (SMR = 0.6), lymphosarcoma and reticulosarcoma (SMR = 0.4), all accidents (SMR = 0.6), and motor vehicle accidents (SMR = 0.6). We observed a slightly elevated relative risk for lung cancer (SMR = 1.2). In general, the SMRs for various causes of death tended to be larger among those unexposed to phenol than those exposed. Mortality from all causes of deaths combined was slightly elevated among

TABLE 1. Distribution of Study Subjects by Exposure Level, Duration of Employment, Age at Entry, and Vital Status for All White Males and White Male Wage Workers

Charac-teristic	White Males		Waged White Males Only			
	All		All		Employed > 1 yr	
	Number	%	Number	%	Number	%
Subjects	14,861	100	12,172	100	7,442	100
Person-year	363,202		293,841		180,389	
Exposure						
None	5,801	39	4,841	40	791	11
Low	4,539	31	3,580	29	2,900	39
Medium	3,627	24	2,983	25	2,983	40
High	894	6	768	6	768	10
Duration (years)						
<1	5,322	36	4,730	39	0	0
1–5	3,319	22	2,660	22	2,660	36
6–10	1,162	8	884	7	884	12
11–15	900	6	672	6	672	9
16–20	1,031	7	813	7	813	11
>20	3,127	21	2,413	20	2,413	32
Year of entry						
≤1945	2,937	20	2,181	18	1,676	23
1946–1955	7,703	52	6,607	54	3,586	48
1956–1965	4,221	28	3,384	28	2,180	29
Age at entry (years)						
≤30	10,720	72	8,746	72	5,274	70
31–40	2,837	19	2,318	19	1,458	20
41–50	1,161	8	1,000	8	635	9
>51	143	1	108	1	75	1
Vital status						
Alive	11,357	76	9,153	75	5,618	76
Deceased	3,102	21	2,667	22	1,696	23
Unknown	405	3	355	3	130	1

nonexposed subjects (SMR = 1.1), but was slightly depressed among exposed subjects (SMR = 0.9). We observed excesses of mortality among the nonexposed for diseases of the circulatory system (SMR = 1.1) and arteriosclerotic heart disease (SMR = 1.1), while slight deficits occurred among the exposed.

We found higher SMRs among nonexposed workers compared with exposed workers for all causes of death; all cancers; cancers of the buccal cavity and pharynx, stomach, liver, pancreas, larynx, lung, testis, brain and central nervous system; diseases of the circulatory system; arteriosclerotic heart disease; emphysema; diseases of the digestive system; cirrhosis of the liver; all accidents; and motor vehicle accidents. No important excesses for specific diseases occurred among the phenol-exposed group, but higher SMRs occurred among those exposed to phenol for cancers of the esophagus, rectum, skin, bladder, kidney; lymphosarcoma; and Hodgkin's disease.

Of those diseases, the SMRs among phenol-exposed white males were greater than 1.0 for cancers of the esophagus (SMR = 1.6), bladder (SMR = 1.1), and kidney (SMR = 1.3), and for Hodgkin's disease (SMR = 1.7). Similar mortality patterns were observed among white wage-earning male workers and white wage-earning male workers employed more than a year. For the latter, an excess mortality (SMR = 1.2) among the phenol-exposed group was observed for lung cancer, whereas a deficit (SMR = 0.7) was seen among the nonexposed group.

Mortality among white males by level of cumulative exposure to phenol is shown in Table 3. Cancer of the esophagus, lung, and liver showed positive but inconsistent associations with cumulative exposure to phenol. All the other cancer sites showed no dose–response relation with exposure to phenol. On the other hand, arteriosclerotic heart disease, emphysema, and cirrhosis of the liver showed declining trends with cumulative exposure to phenol. Weak inverse associations were also observed for cancers of the larynx and brain.

The standardized rate ratios showed patterns similar to those found for SMRs for arteriosclerotic heart disease, emphysema, and cirrhosis of the liver by cumulative exposure to phenol.

In addition to the index of cumulative exposure, we also evaluated the effect of duration of exposure and the potential for dermal contact on risk. Similar declining mortality patterns were observed with increasing duration of exposure and potential of dermal contact. For duration of exposure, SMRs at no-, low-, medium-, and high-exposure categories were 1.2, 0.9, 1.1, and 0.9 for arteriosclerotic heart disease; 1.5, 1.4, 0.6, and 0.7 for emphysema; and 1.3, 1.0, 0.7, and 0.6 for cirrhosis of the liver, respectively. For dermal contact, SMRs were 1.1, 1.0, 1.0, and 0.7 for arteriosclerotic heart disease; 1.2, 1.2, 1.0, and 0.0 for emphysema; and 1.2, 0.9, 0.6, and 0.6 for cirrhosis of the liver, respectively. The results of the analyses for other causes of death were similar to those of cumulative exposure.

Discussion

In this study, industrial workers exposed to phenol showed rates of mortality from all causes combined that were about as expected. No strong healthy worker effect was observed in the overall mortality. Deficits in mortality occurred for infective and parasitic diseases and for accidents among phenol-exposed and nonexposed groups. These causes of deaths often show deficits for working populations compared with a general population.[13,14]

Mortality from all cancers combined did not appear to be related to phenol exposure. The excess mortality from

TABLE 2. Cause-Specific SMR for Exposed and Nonexposed White Male Workers

Cause of Death (ICD-8th)	Observed	SMR	95% CI	Cause of Death (ICD-8th)	Observed	SMR	95% CI
All causes (1–999)	3,102	1.0	0.9–1.0	**All cancers (continued)**			
Nonexposed	1,101	1.1	1.1–1.2	Kidney (189)	17	1.1	0.7–1.8
Exposed	2,001	0.9	0.9–1.0	Nonexposed	4	0.8	0.2–2.1
All infective and parasitic				Exposed	13	1.3	0.7–2.1
diseases (1–139)	30	0.6	0.4–0.9	Brain (191–192)	18	0.9	0.5–1.4
Nonexposed	9	0.6	0.3–1.0	Nonexposed	8	1.1	0.5–2.1
Exposed	21	0.7	0.4–1.0	Exposed	10	0.7	0.4–1.4
All cancers (140–209)	611	1.0	0.9–1.1	Lymphosarcoma/			
Nonexposed	194	1.1	0.9–1.2	reticulosarcoma (200)	5	0.4	0.1–0.9
Exposed	417	1.0	0.9–1.2	Nonexposed	1	0.2	0.0–1.2
Buccal cavity and pharynx				Exposed	4	0.4	0.1–1.1
(140–149)	18	0.9	0.6–1.5	Hodgkin's disease (201)	12	1.2	0.6–2.1
Nonexposed	7	1.2	0.5–2.4	Nonexposed	2	0.5	0.1–1.9
Exposed	11	0.8	0.4–1.5	Exposed	10	1.7	0.8–3.1
Esophagus (150)	19	1.4	0.8–2.2	Leukemia (204–207)	21	0.9	0.5–1.4
Nonexposed	4	1.0	0.3–2.5	Nonexposed	7	0.9	0.3–1.8
Exposed	15	1.6	0.9–2.6	Exposed	14	0.9	0.5–1.4
Stomach (151)	28	0.9	0.6–1.3	**Diseases of circulatory system**			
Nonexposed	10	1.1	0.5–1.9	(390–458)	1,502	1.0	0.9–1.1
Exposed	18	0.8	0.5–1.3	Nonexposed	497	1.1	1.0–1.2
Colon (153)	46	0.9	0.7–1.2	Exposed	1,005	0.9	0.9–1.0
Nonexposed	13	0.9	0.5–1.5	**Arteriosclerotic heart disease**			
Exposed	33	0.9	0.6–1.3	(410–413)	1,103	1.1	0.9–1.1
Rectum (154)	24	1.3	0.8–1.9	Nonexposed	356	1.1	1.0–1.2
Nonexposed	6	1.1	0.4–2.4	Exposed	747	1.0	0.9–1.1
Exposed	18	1.4	0.8–2.2	**Emphysema (492)**	42	1.1	0.8–1.5
Liver (155–156)	12	1.0	0.5–1.8	Nonexposed	16	1.5	0.9–2.4
Nonexposed	4	1.2	0.3–2.9	Exposed	26	0.9	0.6–1.3
Exposed	8	1.0	0.4–1.9	**Diseases of digestive system**			
Pancreas (157)	22	0.7	0.4–1.1	(520–577)	143	0.9	0.7–1.0
Nonexposed	8	0.8	0.4–1.7	Nonexposed	66	1.2	0.9–1.6
Exposed	14	0.6	0.4–1.1	Exposed	77	0.7	0.6–0.9
Larynx (161)	13	1.5	0.8–2.5	**Cirrhosis of liver (571)**	83	1.0	0.8–1.2
Nonexposed	6	2.2	0.8–4.9	Nonexposed	39	1.3	0.9–1.8
Exposed	7	1.1	0.5–2.3	Exposed	44	0.8	0.6–1.0
Lung (162–163)	216	1.2	1.0–1.3	**All accidents (800–949)**	175	0.6	0.6–0.7
Nonexposed	70	1.2	1.0–1.5	Nonexposed	81	0.7	0.6–0.9
Exposed	146	1.1	0.9–1.3	Exposed	94	0.6	0.5–0.7
Skin (172–173)	10	0.8	0.4–1.5	**Motor vehicle accidents**			
Nonexposed	3	0.7	0.2–2.0	(810–827)	83	0.6	0.5–0.8
Exposed	7	0.9	0.4–1.8	Nonexposed	47	0.8	0.6–1.1
Prostate (185)	31	1.0	0.7–1.4	Exposed	36	0.5	0.3–0.7
Nonexposed	8	1.0	0.4–2.0				
Exposed	23	1.0	0.6–1.4				
Testis (186–187)	5	1.0	0.3–2.3	**No. of persons**			
Nonexposed	3	1.4	0.3–4.1	Nonexposed		13,610	
Exposed	2	0.7	0.1–2.4	Exposed		9,042	
Bladder (188)	16	1.0	0.6–1.6	**No. of person-years**			
Nonexposed	3	0.7	0.1–2.0	Nonexposed		150,418	
Exposed	13	1.1	0.6–1.4	Exposed		212,784	

lung cancer and other cancer sites showed no clear dose–response relation by any exposure index. Phenol is an unlikely agent for these small cancer excesses and deficits owing to the lack of consistent pattern of risk with cumulative exposure.

An unexpected finding is that mortality from arteriosclerotic heart disease, emphysema, and cirrhosis of the liver showed declining SMR and SRR trends with cumu-

lative exposure to phenol. Other exposure indices, such as duration of exposure and potential of dermal contact, showed similar patterns for these three causes of death.

Occupational studies frequently reveal a healthy worker effect, that is, a lower mortality rate in industrial workers relative to the general population, that is a source of confounding bias.[15] Several methods have been suggested to control this sort of bias in epidemiologic studies.[16,17] In

TABLE 3. Mortality from Selected Causes of Death by Level of Cumulative Exposure to Phenol among White Males

	Level of Cumulative Exposure to Phenol							
	None		Low		Medium		High	
Causes of Deaths	Observed	SMR	Observed	SMR	Observed	SMR	Observed	SMR
Cancer of:								
Buccal cavity and pharynx (140–149)	7	1.2	3	0.5	7	1.2	1	0.8
Esophagus (150)	4	1.0	4	0.9	10	2.3	1	1.1
Stomach (151)	10	1.1	11	1.0	5	0.5	2	1.1
Rectum (153)	6	1.1	9	1.4	9	1.5	0	—
Liver (155–156)	4	1.2	1	0.3	6	1.6	1	1.4
Larynx (161)	6	2.2	4	1.4	3	1.1	0	—
Lung (162–163)	70	1.2	68	1.2	60	1.1	18	1.4
Skin (172–173)	3	0.7	4	1.0	2	0.6	1	1.7
Bladder (188)	3	0.7	5	1.0	8	1.5	0	—
Kidney (189)	4	0.8	7	1.5	5	1.1	1	1.0
Brain (191–192)	8	1.1	7	1.0	3	0.5	0	—
Hodgkin's (201)	2	0.5	8	2.3	2	0.9	0	—
Leukemia (204–207)	7	0.9	8	1.0	5	0.7	1	0.8
Arteriosclerotic heart disease (410–413)	356	1.1	354	1.0	333	1.0	60	0.9
Emphysema (492)	16	1.5	15	1.2	10	0.8	1	0.3
Cirrhosis of liver (571)	39	1.3	25	0.9	17	0.7	2	0.4
No. persons	13,610		8,655		4,483		880	
No. of person-years	150,418		128,979		74,316		9,487	

this study, we calculated the age-adjusted, directly standardized rate ratios (SRR) for each exposure category, using the rate of the nonexposed group as a comparison group to control for the healthy worker effect. The declining SRRs for arteriosclerotic heart disease, emphysema, and cirrhosis of the liver with increasing cumulative exposure to phenol indicate that the healthy worker effect is an unlikely explanation for these findings.

Most of the study subjects were also exposed to a number of other chemicals in addition to phenol and formaldehyde. These included asbestos, urea, melamine, hexamethylenediamine, wood dust, plasticizers, carbon black, ammonia, antioxidants, and others. It seems unlikely, however, that exposure to these substances would confound the inverse association observed.

Phenol is a normal constituent of the human environment and the human body.[18] Phenol is oxidized by phenol oxidase, a cytochrome p-450, to hydroquinone, which further oxidizes to benzoquinone. The hydroquinone ↔ benzoquinone oxidation-reduction (redox) reaction is a reversible reaction, which could play a role in modulating cellular oxidative metabolism.[19] Quinone/hydroquinone pairs, including vitamin K, vitamin E, and coenzyme Q, are easily oxidized or reduced, serving as either one or two electron acceptors or donors. The hydroquinone form could contribute to a cellular defense mechanism by reacting rapidly with free radicals and serving as free-radical "chain terminators." Thus, the following chain of

molecular events may be postulated as an explanation for our epidemiologic observations: (1) exposure to phenol, (2) increase in endogenous levels of phenol/hydroquinones, (3) increase in free-radical trapping by the quinone family, and (4) decrease in mortality from diseases induced by free radicals.

Consistent with this series of events, inflammatory cells, including polymorphonuclear leukocytes and macrophages, are particularly effective in generating a spectrum of oxygen-derived oxidants.[20] Such cells have been implicated in the pathogenesis of a number of disease states, including atherosclerosis[21] and emphysema.[22] Phenol and hydroquinone have been shown to interfere with the generation of oxidants by these cells.[19]

Work with animals on the interrelation between arteriosclerosis and aldehydes, and hydroquinone (a phenol metabolite) has suggested that "hydroquinone, formaldehyde and acetaldehyde have preventive effects against the development of experimental arteriosclerosis."[23] Another animal study showed that phenol has a strong inhibitory effect on platelet aggregation in blood,[24] and it increases the coronary flow and lowers the blood pressure.[25]

Although experimental biochemical and toxicological studies are suggestive of a protective effect of phenol, other epidemiologic evidence is lacking. In a nested case-control study from a rubber industry cohort evaluating the chronic effect of phenol, Wilcosky and Tyroler

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observed a positive association between phenol exposure and ischemic heart disease.[26] Another nested case-control study evaluating respiratory cancers and chemical exposure found elevated odd ratios for phenol exposure.[27] These effects were partly explained by smoking and exposure to pesticides, which seem to confound the observed association for phenol exposure.

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